Clin Kidney J (2012) 5: 431–433
doi: 10.1093/ckj/sfs099
Advance Access publication 6 September 2012

Clinical Report

CKJ

Acute kidney injury in a preterm infant homozygous for the C3435T polymorphism in the *ABCB1* gene given oral morphine

Laura Pogliani[1], Chiara Mameli[1], Dario Cattaneo[2], Emilio Clementi[2,3], Fabio Meneghin[1], Sonia Radice[2], Simona Bruno[4] and Gian Vincenzo Zuccotti[1]

[1]Department of Pediatrics, L. Sacco Hospital, University of Milan, Milan, Italy, [2]Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, Consiglio Nazionale delle Ricerche Institute of Neuroscience, L. Sacco Hospital, University of Milan, Milan, Italy, [3]E. Medea Scientific Institute, Bosisio Parini, Italy and [4]Castelli Clinic, Bergamo, Italy

Correspondence and offprint requests to: Laura Pogliani; E-mail: laura_pogliani@libero.it

Abstract

A 34-week infant born from a mother with a history of drug abuse developed neonatal abstinence syndrome (NAS) in the first hours of life. Urine drug screening was positive for cocaine and heroin. The infant developed acute kidney injury and bilateral hydronephrosis while receiving oral morphine for control of NAS. Cessation of morphine therapy and urinary catheterization resulted in a rapid and complete resolution of the symptoms. Our patient was homozygous for the C3435T polymorphism in the *ABCB1* gene, a polymorphism previously associated with impaired P-glycoprotein activity. We hypothesize that acute renal toxicity was related to accumulation of morphine within urothelial cells due to genetically determined impaired P-glycoprotein activity.

Keywords: acute kidney injury; morphine; pharmacogenetics; preterm infant

Introduction

Morphine is frequently used to relieve pain and achieve sedation in many age groups. In preterm infants, morphine is largely used for pain control in neonatal intensive care units and for the management of the neonatal abstinence syndrome (NAS). Despite its recognized benefits, the use of morphine is associated with adverse effects on the cardiovascular, gastrointestinal and nervous systems such as hypotension, bradycardia, seizures, decreased gastrointestinal motility, intestinal obstruction and respiratory depression [1, 2]. Renal side effects of morphine (urethral spasm, spasm of bladder sphincters, urinary retention or hesitancy, antidiuretic effect and rhabdomyolysis) have been previously reported in adult patients [3, 4]. Little is however known about the adverse kidney effects of morphine on paediatric patients and, in particular, in preterm infants [1, 2, 5, 6].

Studies in adults indicate that peripheral mechanisms may play a role in opioid-induced bladder dysfunction and urinary retention [7, 8]. However, the exact mechanism by which morphine causes urinary retention and renal impairment in premature infants is unknown. Age-related difference in morphine clearance may contribute to the observed different response to opioid therapy from infancy to adulthood [9–11]. Additionally, the pharmacokinetics and pharmacodynamics of morphine are influenced by several polymorphic genes [12]. Preliminary data suggest that variation in genes coding the drug-metabolizing enzyme (*UGT2B7*), mu-opioid receptors (*OPRM1*), the enzyme degrading catecholamines (*COMT*) and intracellular drug accumulation by P-glycoprotein (*ABCB1*) can significantly influence the clinical outcome of patients given morphine therapy [13–16]. Despite this, the pharmacogenetics of morphine have not been previously considered in the paediatric population as an explanation for poor drug response and/or for drug side effects.

We report a case of acute kidney injury and bilateral hydronephrosis in a premature infant homozygous for the C3435T polymorphism in the *ABCB1* gene treated with oral morphine. We believe that this is the first published report demonstrating a relationship between renal morphine toxicity and genetic background in paediatric patients.

Case report

A 2240 g Caucasian male neonate was born at 34 weeks of gestation by emergency caesarean section performed for premature rupture of membrane. The mother was HIV-positive and had a history of cocaine and heroin abuse throughout her pregnancy. Apgar scores at 1 and 5 min after birth were 6 and 8, respectively. One hour after birth, the infant developed an NAS characterized by central nervous system irritability, tremors, poor feeding, exaggerated Moro reflex, increased muscle tone and uncoordinated sucking. His Finnegan Score (which comprehensively scores all relevant clinical signs of NAS in newborn infants during the first days of life assessing central nervous system hyperirritability, gastrointestinal

Table 1. Time course of the main biochemical and clinical parameters observed in our patient

Parameters	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	At discharge	Normal values
S. creatinine (μmol/L)	77.8	—	85.7	—	—	82.2	93.7	79.6	71.6	—	46.9	50–100
Urine output (mL/kg/h)	Wet diaper[a]	Wet diaper[a]	Wet diaper[a]	~3	~2.0	3.0	[b]	2.7	3.0	2.5	4.0	>1–2
S. potassium (mmol/L)	3.9	4.0	3.5	3.9	4.1	5.3	6.2	4.6	4.2	4.6	4.1	3.5–5.0
Morphine dose (mg/kg/24 h)	0.5	0.7	0.6	0.4	0.4	0.3	Interrupted	—	—	—	—	
Finnegan's score	12	11	4	6	6	5	4	8	4	4	2	<8

[a]The patient was not catheterized and no quantitative assessment was performed.
[b]Urinary catheterization performed, residual volume 73 mL.

dysfunction, respiratory distress and vague autonomic signs in a semi-quantitative way [17]) yielded a result of >12 (a Finnegan score of 8 or higher is considered severe and requires medical therapy).

A urine test performed soon after birth was positive for cocaine and heroin. Treatment with oral morphine was immediately started (0.5 mg/kg/24 h in four divided doses given every 6 h and then decreased to 0.4 mg/kg/24 h in three divided doses given every 8 h). To reduce the risk of vertical HIV transmission, oral zidovudine was started at 6 h of life. On Day 5, urine output decreased gradually and the serum creatinine level increased from 77.8 to 93.7 μmol/L (from 0.88 to 1.06 mg/dL) on Day 7 (Table 1). The potassium level rose concomitantly from 4.1 to 6.2 mmol/L (from 4.1 to 6.2 meq/L), whereas sodium remained normal without the development of metabolic acidosis. Physical examination revealed hypotonia, lethargy, distended abdomen and a vesical globe. A renal ultrasound showed bladder distension with bilateral hydronephrotic kidneys [bipolar length 4.5 cm (normal for age 3–4 cm)]. Urinary catheterization drained 73 mL of straw-coloured urine with resolution of the bladder distension. Morphine was discontinued without rebound or adverse effects and over the subsequent 3 days, renal function returned to normal (Table 1). Repeat ultrasound confirmed the resolution of hydronephrosis.

An additional blood sample was collected for pharmacogenetic analyses (after informed consent was obtained from the mother). According to pyrosequencing analysis, the patient was wild type for the most common allelic variants of *UGT2B7*, *OPRM1* and *COMT* genes. However, he was homozygous for the C3435T (rs1045642) polymorphism of the ABCB1 gene that has been previously associated with absent/impaired P-glycoprotein activity [18].

The infant was discharged on Day 33: no further urinary retention was observed during hospitalization. Oral zidovudine therapy was continued for 6 weeks after birth and was well tolerated. The infant was followed during the first 18 months of life to monitor growth and renal development: no sign of renal impairment was reported and the transmission of HIV infection was excluded.

Discussion

A few cases of acute kidney injury and hydronephrosis have been reported in the literature after opioid administration in preterm infants [5, 6]. To our knowledge, this is the first case in which a possible pharmacogenetic cause has been identified. Other important causes of acute kidney injury bladder distension and hydronephrosis, such as urological malformations, neoplasia, vesicoureteral reflux and neurogenic bladder, were excluded in this case. The renal impairment was also reversible and improved soon after discontinuation of morphine. The clinical evidence thus suggests a pathophysiological mechanism related to morphine. Nevertheless, the possibility that other as yet unknown factors may be involved cannot be excluded.

Our patient was homozygous for a polymorphic variant in position 3435 of the *ABCB1* gene. This gene encodes for P-glycoprotein, a protein that belongs to the ABC transporter family and is expressed in leucocytes, hepatocytes, blood–brain barrier and mainly on the brush border of enterocytes and renal tubular cells [18]. Importantly, P-glycoprotein is also expressed in urothelial cells [19–22], playing a key role in the disposition of chemotherapy in urothelial cancers [19, 21]. Our patient experienced acute kidney injury and bilateral hydronephrosis while receiving oral morphine for the control of NAS. This resolved after urinary catheterization, suggesting that the site of the obstruction was the bladder neck. We hypothesize that acute renal toxicity was related to accumulation of morphine and its metabolite within urothelial cells due to genetically determined, impaired P-glycoprotein activity.

A potential limitation is that we did not measure the plasma concentrations of morphine and its main glucuronide metabolite. However, studies showing the impact of C3435T polymorphism in the *ABCB1* gene on clinical outcomes have consistently failed to demonstrate an association with blood drug concentrations, suggesting a local (rather than systemic) effect on drug disposition [15, 23]. P-glycoprotein is an efflux transporter that actively transports lipophilic drugs from the intracellular to the extracellular domain. Consequently, reduced expression and/or altered activity of P-glycoprotein can increase the intracellular and tissue drug concentrations, ultimately resulting in local drug toxicity.

Studies aimed at investigating the role of ABCB1 polymorphisms on morphine efficacy and/or safety have provided conflicting results. Some studies have reported significant associations between allelic T variants of ABCB1 with morphine-induced adverse gastrointestinal and central drug reactions in adults patients with cancer [14, 15], whereas other investigators have failed to document a role of genetic factors with morphine response [24–26]. No clinical studies have previously addressed the role of ABCB1 polymorphisms on morphine-related

kidney injury and our single case report does not provide a definitive conclusion on this topic. Nevertheless, we believe that it provides an intriguing mechanistic hypothesis that needs further investigation.

Conclusion

Pain and NAS in newborns are therapeutically managed by the administration of opioids. Morphine is one of the most important and widely used opioids in neonatology; but, large variability in its efficacy and/or safety represents a major clinical challenge. Clinical pharmacology studies in adults have demonstrated the importance of pharmacogenetics in determining the response to drug therapy [27–29]. Our observation is in line with these data and suggests that pharmacogenetics can aid our understanding of morphine-induced adverse effects in neonates as in other age groups.

Acknowledgements. Funding. The financial support by Regione Lombardia (MEAP project, Monitoraggio degli eventi avversi in pediatria) is gratefully acknowledged.

Conflict of interest statement. None declared.

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Received for publication: 23.4.12; Accepted in revised form: 13.7.12